IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	10/646,970
Applicant	:	Carol J. Phelps
Conf. No.	:	3048
Filed	:	August 21, 2003
TC/A.U.	:	1632
Examiner	:	Magdalene K. Sgagias
Title	:	Porcine Animals Lacking Any Expression of Functional Alpha 1,3 Galactosyltransferase
Docket No.	:	10758.105009 REV1004
Customer No.	:	20786

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

November 9, 2009

Declaration under 37 C.F.R. §1.131

1. I am the sole named inventors of the invention claimed in the above-referenced patent application.
2. In a final Office Action mailed by the U.S. Patent and Trademark Office on June 2, 2009, the Examiner rejected Claims 1-8, 13, 17-18, 43, 48, 60 and 62 under U.S.C. 102(e) as anticipated by Hawley, et al. (US Publication No. 2006/0242722, filed August 14, 2003 and claiming priority to U.S. Provisional Application No. 60/403,405, filed August 14, 2002).
3. I conceived of the pigs lacking α(1,3)galactosyltransferase (GT) before August 14, 2002. Furthermore, these pigs were actually born prior to the reference date. The work leading to this invention was carried out in the US at PPL Therapeutics Inc.'s US subsidiary located in Blacksburg, Virginia.
4. Exhibits 1-3 are submitted to support the actual reduction to practice of the invention prior to the reference date. Exhibit 1, attached to this declaration, is a press release from PPL Therapeutics that notes that double knockout pigs lacking both copies of the GT gene were born on July 25, 2002. These pigs were thus actually reduced to practice prior to August 14, 2002.
5. Exhibit 2 shows images of lectin staining of liver of wild type pigs and the liver of one of the pigs born on July 25, 2002 (coded "761-1"). Lectin stains to the α-(1,3)-galactose sugar residue in cell components. In essence, the image shows a complete lack of staining in the

761-1 pig (right panels), but diffuse sinusoidal (small arrow upper left), venous endothelial (large arrow upper left), and biliary epithelial cell (large arrow bottom left) in the wild type pig. The higher magnification of 761-1 (lower right) shows in greater detail the absence of biliary epithelial cell or venous endothelial cell staining.

6. Exhibit 3 is a copy of Phelps, et al. (2003) *Science* 299:411-414 and its supplementary materials (see reference on page 414), which includes additional studies showing that cells from the animals born prior to August 14, 2002 did not express any functional GT, as recited in the claims.
7. I declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. I acknowledge that willful false statements are punishable by fine or imprisonment or both under 18 U.S.C. §1001 and may jeopardize the validity of the application or any patent issuing thereon.

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Carol J. Phelps Date

Exhibit 1

Date: Immediate: Thursday 22 August 2002

PRESS RELEASE

Contact: Dr. David Ayares, COO and VP of Research
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PPL THERAPEUTICS PLC

WORLD'S FIRST CLONED DOUBLE KNOCK-OUT PIGS LACK BOTH COPIES OF GENE INVOLVED IN HYPERACUTE REJECTION IN HUMANS

Blacksburg, Virginia: PPL Therapeutics Plc ("PPL"), one of the leading biopharmaceutical companies in the application of transgenic technologies is pleased to announce it has produced the World's first double gene 'knock-out' piglets which were born as a result of using PPL's proprietary gene targeting technology and nuclear transfer (cloning). Earlier this year PPL announced the birth of pigs in which a single copy of the alpha 1,3 galactosyl transferase (GT) gene had been knocked out - the single 'knock-out' pigs. This development is an extension of that work.

Four healthy piglets were born at PPL Therapeutics Inc, USA on 25 July, 2002 and continue to do well. A fifth piglet died shortly after birth of unknown causes. The gene that has been double 'knocked-out' in these pigs is responsible for making an enzyme that adds a sugar to the surface of pig cells which is recognised by the human immune system as foreign. This pig sugar (alpha 1,3 galactose) triggers an immune response in the human patient, leading to hyperacute rejection of the transplanted organ or cell within minutes. The ability to delete or 'knock-out' both copies of the gene, therefore, provides a vital step in producing pigs with organs and cells which can be used in humans. Because both copies of the gene have been inactivated, tissues from these pigs have been shown to be completely devoid of the pig sugar that cause the hyperacute rejection to take place.

As announced earlier in the year, PPL is in the process of 'spinning out' its regenerative medicine program (xenografts and stem cells), of which the knock-out pig program is part, in order to focus its resources on its lead protein products, recAAT for hereditary emphysema, Fibrin 1, and BSSL. It is also the Board's belief that the resources required to bring a product to market in the area of regenerative medicine will be significant and beyond the current resources of PPL. The announcement today, however, recognises another key milestone for PPL in the area of xenotransplantation and demonstrates the company's leading-edge position in this rapidly developing field. The company intends to have completed the spin-out by the end of the year.

As part of PPL's ongoing collaboration with the University of Pittsburgh's Thomas E. Starzl

Transplant Institute, organs and cells from these double knock-out pigs will be used in pivotal transplantation studies aimed at testing for elimination of hyperacute rejection and long term survival of these xenografts.

The 'knock-out' work was carried out by PPL Therapeutics Inc, PPL's US subsidiary located in Blacksburg, Virginia, and was partly supported by an ATP Grant from the US Government's National Institute of Standards and Technology (NIST). In addition to these double knock-out pigs, the company has generated more than 60 male and female single gene GT knock-out pigs since the first litter was born in December 2001, demonstrating that this technology is now a reliable and reproducible tool for making very precise genetic changes in these animals.

David Ayares, COO and VP of Research at PPL Therapeutics Inc said:
"This advance brings us closer to the promise of a potential solution to the world-wide shortage of organs and cells for transplantation."

Geoff Cook, Chief Executive Officer said:
"This is an important step for PPL demonstrating our leading position in this exciting area. The news will support our efforts in spinning out PPL's regenerative medicine business, that will then enable us to focus on our core protein work."

- Ends -

Notes to Editors:

1. **PPL Therapeutics is a biopharmaceutical company which is one of the world's leaders in the application of transgenic animal technologies to the development and production of human proteins for therapeutic and nutritional applications. PPL's three lead products are Alpha-1-Antitrypsin (AAT), fibrinogen and bile salt stimulated lipase (BSSL). PPL is the only company to offer a wide range of animals for transgenic protein production, including sheep, cows, rabbits and pigs.**

2. Xenotransplantation is the transfer of cells, tissues, or organs from one species to another. The fundamental problem with transferring organs between species is rejection by the recipient's immune system. PPL's comprehensive xenograft program relates to both its technology and its Intellectual Property portfolio. In addition to overcoming early hyperacute rejection, the company has also shown proof-of-concept, and has filed patent applications relating to solutions for all aspects of xenograft rejection including delayed xenograft refection, coagulopathy, and chronic T cell mediated rejection. Thus the double 'GT knock-out' pig will serve as the platform for adding up to three more genes, and include a T cell tolerance regime, in order to address all stages of rejection.

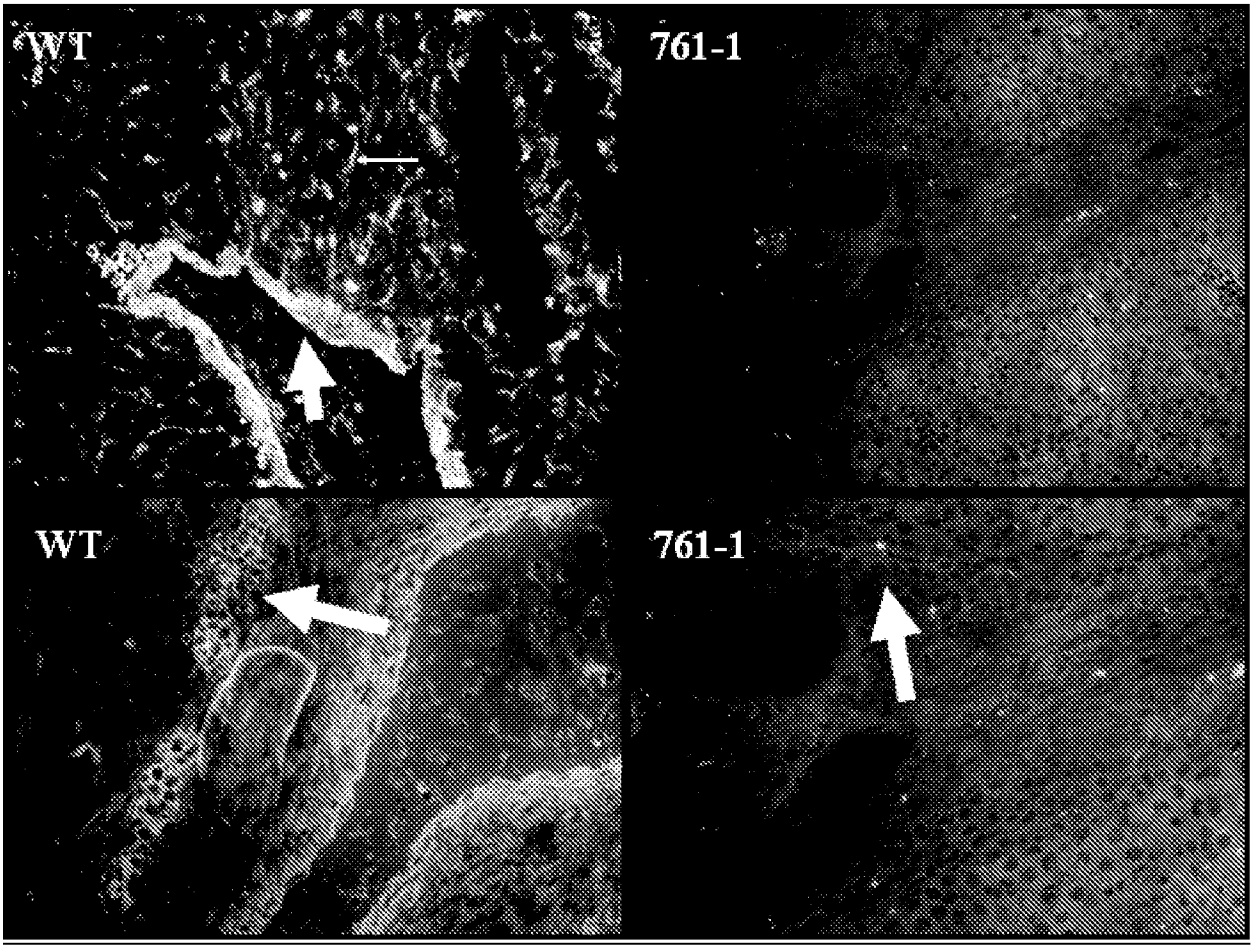
3. In addition to its xenograft program, PPL has an advanced stem cell program which holds the promise of providing a human cell-based solution to diabetes, neurological and cardiovascular disease. The company received a second ATP grant from NIST in January 2001 for $2 million to fund its proprietary research on the generation of "ethical" stem cells. This method involves the de-differentiation of somatic cells to become ES-like cells, and has the advantage that no embryos are created or destroyed at any point in the process. This technology has the potential to provide a solution to the shortage of stem cell lines for therapeutic applications.

4. The first application of this technology could be the testing of insulin-producing islet cells for the treatment of Type I Diabetes from the 'double knock-out' pigs, first in animals, and thereafter in humans. Testing of pig organs (heart and kidney) could follow after the first cell experiments. Human clinical trials could start in two to four years.

5. The US division of PPL also has a 3-year, $3.1 million contract with the US Dept. of Defence for biological warfare countermeasures. As part of this DARPA-funded program, the company is utilising its proprietary cloning and gene targeting technology to inactivate all the cow antibody-producing genes, and replacing them with human equivalents, in order to make large volumes of fully-human polyclonal antibodies, in cattle, as a means of immunising soldiers and civilians against biological warfare pathogens such as anthrax.

6. For additional information visit PPL's web site: www.ppl-therapeutics.com

Exhibit 2


WT
761-1
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761-1

Exhibit 3

See attached